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Appl. No. 10/766,096
Amdt. dated July 19, 2006
Reply to Office Action of May 2, 2006

REMARKS**I. Status of the Claims**

Claims 1-30 were originally filed in the parent application. This application was filed along with a preliminary amendment, which canceled claims 1-13 and 18-30. Claims 14-17 are pending under examination.

Upon entry of the present amendment, new claims 31-39 are added. These claims find support in original claims 19-27, respectively. Claim 14 is amended to recite a "nucleic acid hybridization assay kit," which finds support in original claim 18, and that the eukaryotic cells are "lyophilized in a RNase-free aqueous, isotonic solution treated with diethyl pyrocarbonate," which finds support in original claims 1 and 2. Claims 15-17 are amended to ensure proper antecedent basis, and claim 17 is amended to delete the language "in an amount effective to reduce degradation of RNA." No new matter is introduced.

II. Claim Objections

The Examiner objected to claims 15-17, alleging that they are of improper dependent form for failing to further limiting the subject matter of a previous claim. Specifically, the Examiner contended that claims 15-17, which are drawn to a "sealed vial of claim 14," cannot properly depend from claim 14, which is drawn to a "collection of ... vials."

In response, claim 14 has been amended to recite a "nucleic acid hybridization assay kit" and claims 15-17 have been amended to recite the "kit of claim 14." Thus, the objection is obviated.

III. Claim Rejections**A. 35 U.S.C. §101**

Claims 14-17 were rejected under 35 U.S.C. §101 for allegedly covering non-statutory subject matter. Specifically, the Examiner stated that, the current language "collection" used in claim 14 falls outside of the categories enumerated in 35 U.S.C. §101.

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In response, claims 14-17 have been amended to recite a "kit" to replace the original language of a "collection" or "vial." Applicants believe this amendment is sufficient to overcome the rejection under 35 U.S.C. §101 and thank the Examiner for his helpful suggestion.

B. 35 U.S.C. §112, Second Paragraph

Claims 14-17 were rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness. More specifically, the Examiner asserted that the terms "collection" and "standardized" in claim 14 is indefinite as to what subject matter is encompassed by these terms. The Examiner also pointed out that claims 15-17 are indefinite, because they are drawn to a "sealed vial of claim 14," since claim 14 is drawn to a "collection of standardized, sealed vials." Furthermore, the Examiner alleged that the language "reduce degradation of RNA" in claim 17 is indefinite.

As amended, claims 14-17 are now drawn to a kit and the inconsistency in antecedent basis is eliminated. Further, the language "reduce degradation of RNA" in claim 17 has been deleted. The withdrawal of the indefiniteness rejection is respectfully requested.

C. 35 U.S.C. §102/103: Kortright *et al.*

Claims 14 and 16 were rejected under 35 U.S.C. §102(b) for alleged anticipation by, or, in the alternative, under 35 U.S.C. §103(a) for alleged obviousness over Kortright *et al.* (U.S. Patent No. 5,059,518). Applicants respectfully traverse the rejection in view of the present amendment and to the extent the rejections may apply to the amended claims.

To anticipate a pending claim, a prior art reference must provide, either expressly or inherently, each and every limitation of the pending claim. MPEP §2131. In order to establish a *prima facie* showing of obviousness, on the other hand, three requirements must be satisfied: all limitations of a pending claim must be expressly or impliedly disclosed by prior art references; there must be a suggestion or motivation in the art for one skilled artisan to combine the limitations; and there must be a reasonable expectation of success in making such a combination. MPEP §2143.

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As amended, the independent claim 14 now recites eukaryotic cells lyophilized in an isotonic aqueous solution that has been treated with diethyl pyrocarbonate (DEPC) and is RNase-free. In contrast, the Kortright reference provides methods for preserving mammalian cells by lyophilization for immunoassays and other hematological measurements. The reference does not explicitly teach a DEPC-treated lyophilizing solution for preserving eukaryotic cells.

The Kortright reference also fails to inherently disclose that the eukaryotic cells are lyophilized in isotonic aqueous solutions that are RNase-free. As described by the court, “in relying upon the theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.” *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Int. 1990). In the present case, no such basis has been provided to support that the cited reference discloses the purported inherent characteristic of lyophilizing cells in an RNase-free isotonic, aqueous solution previously treated with DEPC. Moreover, comparative data provided in the present application demonstrate that no such basis could have been provided to support an anticipation rejection based on inherency theory.

In the Kortright reference, the lyophilized cells are being used for fluorescence activated cell sorting and cytometry, for example, the lyophilized cells are used as controls for immunoassays and other hematological measurements. Thus, the focus of the lyophilization procedure in Kortright is on providing intact proteinaceous molecules and preserving membrane integrity (see, e.g., column 3, lines 25-51 and column 4, lines 35-40). As such, there is no implication in the Kortright reference that the cells were lyophilized in a RNase-free isotonic, aqueous solution treated with DEPC.

Furthermore, the data presented in the example section of the present application demonstrate that the Kortright reference fails to inherently disclose that the carbohydrate (trehalose) lyophilization solution is “nuclease-free.” Example I of the present application provides a comparison of RNA integrity from cells lyophilized either in (1) DEPC-treated water (*i.e.*, nuclease-free but not isotonic) and (2) 1x carbohydrate (lactose) buffer (isotonic but not nuclease-free). Gel electrophoresis analysis of total RNA from the lyophilized cells

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demonstrates that approximately 100% of the total RNA in the 1x lactose sample was degraded, while approximately 50% of the RNA in the DEPC-treated water sample was degraded. The results indicate that lactose and other isotonic carbohydrate formulations (*i.e.*, trehalose) are not sufficient to maintain integrity of RNA in cells lyophilized in such solutions.

In comparison, Example II shows that total RNA isolated from cells lyophilized in DEPC-treated, 1x PBS (nuclease-free and isotonic) was intact as compared to total RNA isolated from freshly grown cells. These examples from the present application therefore demonstrate that lyophilization solutions must be treated so that they are nuclease-free, in order to obtain intact nucleic acid from lyophilized cells.

Thus, the lyophilization procedure in the Kortright reference neither inherently nor explicitly discloses lyophilized cells by using a lyophilization solution that is RNase-free or DEPC treated. Even though the lyophilized cells in Kortright may apparently remain intact, as the experimental data of this application have shown, significant degradation of cellular nucleic acid has taken place. Because the Kortright reference fails to provide at least one limitation of independent claim 14: the use of a DEPC-treated, RNase-free aqueous isotonic solution for cell lyophilization, Applicants submit that claim 14 and its dependent claims cannot be properly rejected for anticipation rejection or obviousness rejection based on Kortright *et al.* The withdrawal of these rejections is therefore respectfully requested.

D. 35 U.S.C. §103: Gallo *et al.* and Kortright *et al.*

Claims 14-17 were rejected under 35 U.S.C. §103(a) for alleged obviousness over Gallo *et al.* (U.S. Patent No. 4,520,113) in view of Kortright *et al.* Applicants respectfully traverse the rejection in view of the present amendment and to the extent the rejection may apply to the amended claims.

As stated above, to establish a *prima facie* showing of obviousness, the Examiner must show that all limitations of a pending claim is expressly or impliedly disclosed by prior art references, there is a suggestion or motivation in references for combining the limitations, and there is a reasonable expectation of success in making the combination. The discussion above

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also indicates that Kortright reference fails to provide at least one limitation of independent claim 14, namely the eukaryotic cells lyophilized in an aqueous isotonic solution that is DEPC-treated and RNase-free. Because the Gallo reference teaches the preparation and use of HIV-producing lymphocytes, and does not supply the missing claim limitation of treating a lyophilizing solution with DEPC to eliminate RNase-contamination, not all limitations of independent claim 14 can be found in the two references.

Furthermore, none of the Kortright and Gallo references identify the cause of nucleic acid instability in lyophilized cells as contamination of exogenous nucleases. Since the cited references fail to reveal this cause, discovery of the cause is an unexpected one made by the inventors of the present application. This surprising discovery leads to the approach of treating lyophilizing solutions with DEPC, which must be regarded as non-obvious under the prevailing case law.

In summary, the combination of the Kortright and Gallo references do not supply all elements of independent claim 14 of the present application. Nor do the references reveal the unexpected cause of nucleic acid degradation in lyophilized cells, which would render the treatment of lyophilizing solutions with DEPC obvious. As such, Applicants submit that the obviousness rejection of claim 14 and its dependent claims based on the Kortright and Gallo references is improper and respectfully request its withdrawal.

E. Double Patenting

Claims 14-17 were further rejected under the judicially created doctrine of double patenting for allegedly being unpatentable over the claims of U.S. Patent No. 6,410,321. Applicants are willing to consider filing a terminal disclaimer once all pending claims are indicated as otherwise allowable.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

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If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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